Cardiac and arterial target organ damage in adults with elevated ambulatory and normal office blood pressure

Cardiac and Arterial Target Organ Damage in Adults with Elevated Ambulatory and Normal Office Blood Pressure

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Background: Ambulatory blood pressure may be higher or lower than clinic blood pressure. Attention has focused on "white coat hypertension" (normal ambulatory blood pressure elevated in the clinic). The converse phenomenon of high ambulatory blood pressure but normal office blood pressure—"white coat normotension"—has not been studied.

Objective: To assess whether white coat normotension (awake ambulatory blood pressure > 134/90 mm Hg and clinic blood pressure < 140/90 mm Hg) is associated with target organ damage.

Design: Cross-sectional observational study.

Setting: University hospital hypertension center and participant work sites.

Patients: 295 clinically normotensive adults and 64 patients with sustained hypertension (elevated clinic and ambulatory blood pressure).

Measurements: Target organ abnormalities were measured by echocardiography and arterial ultrasonography in 61 patients with white coat normotension, 234 with sustained normotension (normal clinic and ambulatory blood pressure), and 64 with sustained hypertension.

Results: Patients with white coat normotension were older; had higher body mass indices, serum creatinine concentrations, and glucose levels; and a higher prevalence of current smokers. Left ventricular mass index and relative wall thickness were higher by 13 g/m^2 (CI, 8 to18 g/m^2) and by 0.03 (CI, 0.01 to 0.04), respectively, in patients with white coat normotension compared with those who had sustained normotension. Patients with white coat normotension and those with sustained hypertension did not differ significantly for left ventricular mass index (4 g/m^2 [CI, −3 to 10 g/m^2) or relative wall thickness (0.01 [CI, −0.01 to 0.03]). The prevalence of discrete atherosclerotic plaques was similar in patients with white coat normotension (17 of 61, or 28% [CI, 17% to 39%]) and those with sustained hypertension (17 of 64, or 27% [CI, 16% to 38%]), but the difference lost significance after adjustment for age.

Conclusions: White coat normotension is associated with left ventricular mass and carotid wall thickness similar to those in sustained hypertension. The association of white coat normotension with prognostically important target organ damage may partly explain the ability of high normal left ventricular mass and high normal clinic blood pressure to predict subsequent hypertension and cardiovascular events in patients with clinical normotension.

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Epidemiologic studies have established that hypertension, detected by clinical blood pressure measurement, is a major contributor to cardiovascular mortality and morbidity (1, 2). Although this relation is highly significant in large populations, only a weak relation exists between blood pressure and likelihood of cardiovascular complications (3). In addition, the factors predisposing normotensive patients to cardiovascular complications have only been partially elucidated. One possible explanation is that office blood pressure readings, on which the existing epidemiologic data are based, may not consistently reflect the overall blood pressure load imposed on the heart and arterial tree because of the wide variations in blood pressure that occur during normal activity.

It is now generally accepted that 24-hour ambulatory blood pressure is more closely associated with target organ damage and future cardiovascular events than isolated blood pressure readings taken in the clinic (4–6). However, a close correlation between clinic blood pressure and left ventricular mass has been reported when multiple readings in well-standardized conditions are done (7, 8). Ambulatory blood pressure may be higher or lower than clinic blood pressure, and attention has been focused on "white coat hypertension" (elevated clinic blood pressure with normal ambulatory blood pressure) (9–11). However, the converse, logically implicit phenomenon of elevated ambulatory blood pressure but normal clinic blood pressure—which may be termed "white coat normotension" (12)—has been reported in a small series (13) but has not been studied in a large population sample.

We sought to 1) determine the prevalence of white coat normotension in large community and clinic samples and 2) to evaluate cardiac and vascular structure in patients classified as having sustained normotension or sustained hypertension according to both clinic and ambulatory blood pressure measurements and in patients classified as having white coat normotension.

Methods

Patients

The study sample was recruited from the Hypertension Center of the New York Hospital–Cornell

Medical Center and from ongoing longitudinal work site–based studies (14, 15). Normotensive persons (age range, 30 to 66 years) were recruited by sampling at defined work sites ($n = 295$); 35 of the patients with sustained hypertension were drawn from the clinical population attending the Hypertension Center and 29 were drawn from the same work sites as normotensive participants. Participants recruited from work sites were enrolled, as described elsewhere (14), by blood pressure screening and subsequent stratification into sex and age groups in which 60% of patients had diastolic blood pressure less than 85 mm Hg and 40% of patients had diastolic pressure of 85 mm Hg or greater. We excluded persons with blood pressure greater than 160/95 mm Hg, those with clinically overt cardiovascular disease, and those who were unwilling to temporarily stop drug therapy. At the Hypertension Center, we recruited consecutive patients with mild hypertension (according to Joint National Committee [JNC] criteria) who were willing to unergo ambulatory blood pressure monitoring and ultrasonography when the laboratories could accommodate them. Normotensive patients had no history of treatment with antihypertensive medications; hypertensive patients either were previously untreated or had not been receiving antihypertensive and other cardioactive drugs for at least 3 weeks and as long as 6 years before study entry. Although the clinic was a smoke-free environment, current smokers were not specifically instructed not to smoke before the examination. All patients were free of clinical evidence of coronary artery or cerebrovascular disease. The presence of valvular disease was excluded by Doppler echocardiography.

A total of 234 patients had sustained normotension on the basis of normal clinic blood pressure ($<$140/90 mm Hg) and awake ambulatory blood pressure ($<$134/90 mm Hg). The latter partition values were chosen because they represented the 90th percentiles of mean daytime systolic and diastolic blood pressure recordings in normal volunteers (16) and were subsequently shown to be useful in identifying patients with white coat hypertension who had little or no target organ damage (10, 11). Sixty-four patients had sustained hypertension (clinic blood pressure $\geq$ 140 mm Hg systolic or $\geq$ 90 mm Hg diastolic; awake ambulatory blood pressure $\geq$ 134 mm Hg systolic or $\geq$ 90 mm Hg diastolic). White coat normotension was identified in 61 patients who had average clinic blood pressure less than 140/90 mm Hg diastolic and awake ambulatory blood pressure of 134 mm Hg or more systolic or 90 mm Hg or more diastolic. Patients with secondary forms of hypertension were excluded. All patients underwent standard blood laboratory analyses, which included a lipid profile and determination of plasma renin activity. Informed consent was obtained under protocols approved by the Committee on Human Rights in Research of Cornell University Medical College.

Blood Pressure

Clinic blood pressure readings were taken by a physician or a nurse on three or more occasions by using an appropriate-sized arm cuff and a mercury sphygmomanometer; values were recorded by using the first and fifth phases of the Korotkoff sounds and were rounded to the nearest 2 mm Hg. As recommended by the fifth report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC-V) (17), clinic blood pressure was determined by taking multiple measurements during at least two different visits, separated by at least 2 weeks, that did not include the first visit; these values were averaged to determine the clinic blood pressure. The schedule was set up so that the patients usually waited 10 to 15 minutes before their blood pressure was measured in the supine position.

In the same study period, ambulatory blood pressure was recorded by having each patient wear a noninvasive ambulatory blood pressure recorder (Space Labs 90207 monitor [Space Labs, Redmond, Washington] with an appropriate-sized cuff) for 24 hours. The monitor was placed on the nondominant arm and was set to take blood pressure readings every 15 minutes during the day and every 30 minutes at night. After each reading, patients recorded their activity and location to allow calculation of 24-hour ambulatory blood pressure while awake, during sleep, at work, and at home. Methods used to validate these readings have been reported elsewhere from this laboratory (16).

Echocardiography

All patients underwent M-mode and two-dimensional echocardiography. The echocardiographs were equipped with 2.5-MHz and 3.5-MHz imaging transducers. The research technician who performed the echocardiography was aware of patients' enrollment source (work site or Hypertensive Center) but not their blood pressure status. Most of the studies were done by using an Acuson 128 echocardiograph (Mountain View, California). Researchers who were blinded to patients' clinical characteristics took left ventricular measurements from two-dimensionally guided M-mode tracings according to recommendations of the American Society of Echocardiography (18) or from linear measurements derived from the two-dimensional study if the M-mode tracings were technically inadequate (19). Measurements were performed on up to six echocardiographic cycles by using a digitizing tablet and were averaged. Left

Table 1. Characteristics of Study Patients*

Characteristic	Patients with Sustained Normotension (n = 234)	Difference in Mean Value between Sustained Normotension Group and White Coat Normotension Group (95% CI)	P Value	Patients with White Coat Normotension (n = 61)	Difference in Mean Value between White Coat Normotension Group and Sustained Hypertension Group (95% CI)	P Value
Age, *y*	44 ± 9	6 (2 to 9)	0.005	50 ± 8	6 (2 to 10)	<0.001
Men/women, *n/n*	126/108		<0.05	11/50		NS
Ethnicity, *n*						
Black	48			13		
White	148			41		
Hispanic	16			5		
Other	21			2		
Height, *in*	66.5 ± 3.4	1.5 (0.3 to 2.8)	0.02	68.0 ± 4.0	1.6 (0.03 to 3.10)	NS
Weight, *lb*	159 ± 28	21 (10 to 32)	<0.001	180 ± 36	17 (3 to 30)	NS
Body surface area, m^2	1.82 ± 0.19	0.13 (0.06 to 0.20)	<0.001	1.95 ± 0.23	0.11 (0.02 to 0.19)	NS
Body mass index, g/m^2	25.2 ± 3.4	1.9 (0.7 to 3.2)	0.008	27.1 ± 3.8	1.2 (−0.3 to 2.8)	NS
Creatinine concentration, *mg/dL*†	0.92 ± 0.16	0.07 (0.009 to 0.13)	0.025	0.99 ± 0.18	0.02 (−0.07 to 0.10)	NS
Cholesterol level, *mg/dL*‡	206 ± 40	22 (8 to 37)	0.001	228 ± 44	2 (−17 to 20)	NS
HDL cholesterol level, *mg/dL*‡	53.4 ± 13.5	1.7 (−3.0 to 6.5)	NS	51.7 ± 13.7	1.4 (−7.5 to 4.7)	NS
Glucose level, *mg/dL*§	79 ± 9	10 (1 to 19)	0.04	89 ± 26	8 (−3 to 19)	NS
Former smokers, *n/n (%)*	67/229 (29)		NS	26/61 (43)		NS
Current smokers, *n/n (%)*	36/229 (16)		NS	14/61 (23)		NS

* Unless otherwise noted, data are presented as the mean ± SD. HDL = high-density lipoprotein; NS = not significant.
† To convert to μmol/L, multiply by 88.402.
‡ To convert to mmol/L, multiply by 0.0259.
§ To convert to mmol/L, multiply by 0.0555.

ventricular mass was calculated by using the Penn convention and was adjusted for body surface area (20). Left ventricular hypertrophy was considered present if the left ventricular mass index (left ventricular mass/height$^{2.7}$) exceeded 49.7 g/m$^{2.7}$ in men or 47.2 g/m$^{2.7}$ in women (21–23). Relative wall thickness, a measure of left ventricular geometry, was calculated as (2 × posterior wall thickness)/end-diastolic dimension. Fractional shortening, ejection fraction, stroke volume, cardiac output, and total peripheral resistance were calculated by using standard formulas.

Carotid Ultrasonography

All patients underwent imaging of both carotid arteries with a Biosound Genesis II system (Esaote Biomedica, Florence, Italy) or an Acuson ultrasonography system equipped with 7.0-MHz to 7.5-MHz imaging transducers, as described elsewhere (15). The patient lay in the supine position with mild hyperextension of the neck to allow optimal visualization of the common carotid artery, carotid bulb, and extracranial internal and external carotid arteries on both sides. Multiple projections were used to identify any irregularity in the vessel walls.

Table 2. Blood Pressure Measurements and Heart Rates in Study Patients*

Measurement	Patients with Sustained Normotension (n = 234)	Difference in Mean Value between Sustained Normotension Group and White Coat Normotension Group (95% CI)	P Value	Patients with White Coat Normotension (n = 61)	Difference in Mean Value between White Coat Normotension Group and Sustained Hypertension Group (95% CI)	P Value
Clinic blood pressure, *mm Hg*						
Systolic	109 ± 10	13 (8 to 17)	<0.001	122 ± 10	ND	
Diastolic	75 ± 7	5 (3 to 8)	0.016	80 ± 6	ND	
Awake blood pressure, *mm Hg*						
Systolic	120 ± 7	ND		139 ± 6	14 (11 to 18)	<0.001
Diastolic	78 ± 6	ND		89 ± 6	6 (3 to 8)	<0.001
Home blood pressure, *mm Hg*						
Systolic	119 ± 8	18 (14 to 21)	<0.001	137 ± 8	14 (10 to 19)	<0.001
Diastolic	76 ± 6	9 (7 to 12)	<0.001	85 ± 5	8 (3 to 9)	<0.001
Sleep blood pressure, *mm Hg*						
Systolic	105 ± 9	11 (8 to 16)	<0.001	116 ± 9	21 (16 to 25)	<0.001
Diastolic	76 ± 7	7 (4 to 10)	<0.001	69 ± 8	11 (7 to 14)	<0.001
Work blood pressure, *mm Hg*						
Systolic	121 ± 8	17 (15 to 21)	<0.001	138 ± 6	13 (8 to 16)	<0.001
Diastolic	79 ± 6	10 (9 to 13)	<0.001	89 ± 6	8 (4 to 8)	<0.001
Heart rate, *beats/min*	69 ± 11	2 (−2 to 6)	NS	71 ± 12	2 (−3 to 7)	NS

* Values are presented as the mean ± SD. ND = not determined; NS = not significant.

Table 1—*Continued*

Patients with Sustained Hypertension ($n = 64$)	Difference in Mean Value between Sustained Normotension Group and Sustained Hypertension Group (95% CI)	*P* Value
56 ± 11	12 (9 to 15)	<0.001
27/37		NS
9		
52		
3		
0		
66.4 ± 3.8	0.1 (−1.2 to 1.3)	NS
163 ± 32	4 (−6 to 15)	NS
1.84 ± 0.22	0.02 (−5.83 to 15.30)	NS
25.9 ± 3.7	0.7 (−0.5 to 1.9)	NS
0.97 ± 0.20	0.05 (−0.01 to 0.12)	NS
230 ± 40	24 (10 to 39)	0.001
53.1 ± 14.0	0.3 (−4.5 to 5.2)	NS
97 ± 53	18 (9 to 27)	<0.005
18/64 (28)		NS
9/64 (14)		NS

Discrete carotid atherosclerosis was defined as the presence of localized plaque, at least 50% greater in thickness than the surrounding wall, on any segment of the arteries (24). A two-dimensionally guided M-mode tracing of the distal common carotid artery, about 1 cm proximal to the carotid bulb, was obtained and was recorded on half-inch super VHS videotape with a simultaneous electrocardiogram. The videotape was subsequently reviewed by researchers who were blinded to patient characteristics, and suitable frames for measurements were obtained by using a frame-grabber (Imaging Technology, Inc., Woburn, Massachusetts), interfaced with a high-resolution (640 × 480 pixel) video monitor, and stored on diskettes. A reader who was blinded to patient characteristics and blood pressures took carotid measurements from the stored images by using a mouse-driven computer program (ARTSS, Cornell University Research Foundation, New York, New York) after calibration for depth and time. Measurements were obtained from several cycles and were averaged. The intimal–medial thickness of the far wall of the distal common carotid artery was measured at end-diastole. Standard wall thickness measurements were never obtained at the level of a discrete plaque. End-diastolic and peak systolic internal dimensions of the artery were determined by continuous tracing of the intimal–lumen interface of the near and far walls of the distal common carotid artery. Relative wall thickness of the artery was calculated according to the formula (2 × end-diastolic wall thickness/end-diastolic dimension). Ultrasonographic characterization of carotid wall layers and measurement of wall thickness have been validated by using gross and histopathologic reference standards (25).

Table 2—*Continued*

Patients with Sustained Hypertension ($n = 64$)	Difference in Mean Value between Sustained Normotension Group and Sustained Hypertension Group (95% CI)	*P* Value
157 ± 21	ND	
96 ± 9	ND	
153 ± 13	ND	
95 ± 10	ND	
151 ± 15	32 (28 to 35)	<0.001
93 ± 10	17 (13 to 19)	<0.001
137 ± 16	32 (29 to 36)	<0.001
81 ± 11	18 (15 to 20)	<0.001
151 ± 12	30 (26 to 34)	<0.001
97 ± 9	18 (16 to 21)	<0.001
69 ± 12	0 (−4 to 4)	NS

Statistical Analysis

Data were stored and analyzed by using the SPSS statistical package (SPSS, Inc., Chicago, Illinois). Continuous, normally distributed variables, expressed as the mean (± SD), were compared among the three patient groups by using analysis of variance followed by post hoc testing with the Scheffe test. Comparisons were also made by using Kruskal–Wallis nonparametric analyses, which confirmed the significance of all reported findings. Analyses of covariance and a logistic regression model were used to adjust for intergroup differences in age, sex, ethnicity, body mass index, diabetes mellitus, serum cholesterol and creatinine levels, and current or previous smoking status; these variables are potential predictors of left ventricular hypertrophy or carotid atherosclerosis. Information on patients' daily ethanol intake was not available. Chi-square statistics with Bonferroni correction for multiple comparisons were used to compare categorical variables between groups. Supplemental analyses in which an indicator variable for the origin of sustained hypertensive patients (work site or Hypertension Center) confirmed the reported results (data not shown). A two-tailed *P* value less than 0.05 was considered statistically significant.

Role of the Funding Source

The National Heart, Lung, and Blood Institute had no role in the collection, analysis, or interpretation of data or in the decision to submit the paper for publication.

Table 3. Left Ventricular Structure and Function in Study Patients*

Measurement	Patients with Sustained Normotension (n = 234)	Difference in Mean Values between Sustained Normotension Group and White Coat Normotension Group (95% CI)	P Value	Patients with White Coat Normotension (n = 61)	Difference in Mean Values between White Coat Normotension Group and Sustained Hypertension Group (95% CI)	P Value
Interventricular septal thickness, *cm*	0.87 ± 0.11	0.09 (0.05 to 0.13)	<0.001	0.96 ± 0.11	0.01 (−0.04 to 0.06)	NS
Left ventricular internal dimension, *cm*	4.80 ± 0.44	0.20 (0.08 to 0.39)	0.008	5.00 ± 0.44	0.06 (−0.11 to 0.28)	NS
Posterior wall thickness, *cm*	0.79 ± 0.11	0.11 (0.07 to 0.15)	<0.001	0.90 ± 0.11	0.02 (−0.04 to 0.06)	NS
Left ventricular mass, *g*	134 ± 33	35 (22 to 48)	<0.001	169 ± 40	3 (−14 to 18)	NS
Left ventricular index, g/m^2	73 ± 14	13 (8 to 18)	<0.001	86 ± 16	4 (−3 to 10)	NS
Left ventricular mass/height$^{2.7}$	32 ± 6	6 (4 to 9)	<0.001	38 ± 8	2 (−1 to 5)	NS
Prevalence of LVH, *n (%)*	1 (0.4)	6.6†	0.001	4 (7)	9†	NS
Relative wall thickness	0.33 ± 0.05	0.03 (0.001 to 0.04)	<0.001	0.36 ± 0.04	0.01 (−0.01 to 0.03)	NS
Fractional shortening, %	36 ± 4	0.002 (−0.01 to 0.02)	NS	37 ± 5	0.02 (−0.003 to 0.04)	0.03
Stroke volume, *mL*	71 ± 17	9 (3 to 15)	0.02	80 ± 19	2 (−6 to 9)	NS
Stroke index, mL/m^2	39 ± 8	2 (−1 to 5)	NS	41 ± 8	2 (−2 to 5)	NS

* Unless otherwise specified, values are presented as the mean ± SD. LVH = left ventricular hypertrophy; NS = not significant.
† Expressed as percentage points.

Results

Study Sample

Characteristics of the study patients are presented in **Table 1**. Of the 295 clinically normotensive patients, the 61 (21%) who met our criteria for white coat normotension were older; were more likely to be male; and had higher body mass indices, serum creatinine concentrations, plasma glucose levels, and total cholesterol levels than patients with sustained normotension. These groups did not differ in distribution of ethnic groups. No statistically significant difference in high-density lipoprotein cholesterol level was seen among the three groups. Patients with white coat normotension were more likely than those with sustained normotension to be current or former smokers, but this difference was not statistically significant.

In contrast, patients with white coat normotension resembled the patients with sustained hypertension in terms of body mass index, creatinine concentrations, and glucose levels. The white coat normotension group contained more men and had a lower mean age than the sustained hypertension group. Patients with sustained hypertension were older than those in the other two groups; they were also less likely to be black than were patients in the sustained normotension group. Sex distribution did not differ between the sustained hypertension group and the sustained normotension group.

Clinic and Ambulatory Blood Pressure

By definition, clinic systolic and diastolic blood pressures were higher in the sustained hypertension group than in the two normotension groups (**Table 2**). Clinic systolic and diastolic blood pressures were significantly higher in the white coat normotension group than in the sustained normotension group. These comparisons remained statistically significant after adjustment for age, ethnicity, and sex. According to JNC-V classification of clinic blood pressure (16), white coat normotension was present in 21 of 44 (48% [95% CI, 35% to 61%]) patients with high normal clinic blood pressure (>130/85 mm Hg but <140/90 mm Hg), 17 of 173 (10% [CI, 6% to 16%]) patients with optimal blood pressure (<120/80 mm Hg), and 23 of 78 (29% [CI, 19% to 30%]) patients with intermediate blood pressure (systolic blood pressure $<$ 130 mm Hg or $\geq$ 120 mm Hg or diastolic blood pressure $<$ 85 mm Hg or $\geq$ 80 mm Hg). As was expected from the defining characteristics of patient groups, mean awake ambulatory blood pressure in patients with white coat normotension fell

Table 4. Carotid Arterial Structure and Function in Study Patients*

Measurement	Patients with Sustained Normotension (n = 234)	Difference in Mean Values between Sustained Normotension Group and White Coat Normotension Group (95% CI)	P Value	Patients with White Coat Normotension (n = 61)	Difference in Mean Values between White Coat Normotension Group and Sustained Hypertension Group (95% CI)	P Value
Wall thickness, *mm*	0.69 ± 0.16	0.10 (0.05 to 0.16)	<0.001	0.79 ± 0.18	0.06 (−0.01 to 0.13)	NS
Lumen diameter, *mm*	5.30 ± 0.59	0.25 (0.05 to 0.50)	0.023	5.55 ± 0.74	0.21 (−0.09 to 0.48)	NS
Cross-sectional area, mm^2	13.1 ± 4.2	3.0 (1.4 to 4.6)	<0.001	16.1 ± 5.3	1.7 (−0.3 to 3.7)	NS
Relative wall thickness	0.26 ± 0.06	0.03 (0.01 to 0.05)	0.004	0.29 ± 0.06	0.01 (−0.02 to 0.03)	NS
Plaque, *n (%)*	35 (15)	14†	<0.05	17 (28)	0.0†	NS

* Unless otherwise indicated, values are presented as the mean ± SD. NS = not significant.
† Expressed as percentage points.

Table 3—*Continued*

Patients with Sustained Hypertension ($n = 64$)	Difference in Mean Value between Sustained Normotension Group and Sustained Hypertension Group (95% CI)	*P* Value
0.97 ± 0.12	0.10 (0.06 to 0.14)	<0.001
4.94 ± 0.50	0.14 (−0.01 to 0.30)	0.017
0.92 ± 0.11	0.13 (−0.04 to 0.06)	<0.001
166 ± 43	32 (20 to 45)	<0.001
90 ± 18	17 (11 to 22)	<0.001
40 ± 9	8 (6 to 10)	<0.001
10 (16)	15.6†	<0.001
0.37 ± 0.05	0.04 (0.02 to 0.06)	<0.001
38 ± 6	2 (−0.003 to 0.04)	0.12
78 ± 18	7 (1 to 13)	NS
42 ± 9	3 (1 to 6)	NS

between that in patients with sustained normotension and that in patients with sustained hypertension. Of note, sleep blood pressures recorded by using an automatic recorder were also higher in patients with white coat normotension than in those with sustained normotension.

Left Ventricular Structure and Function

Left ventricular wall thickness, internal dimension, and relative wall thickness were greater in patients with white coat normotension than in those with sustained normotension (**Table 3**). As a result, absolute left ventricular mass, left ventricular mass index, and left ventricular mass/height$^{2.7}$ were higher in patients with white coat normotension than in those with sustained normotension. In contrast, primary ventricular dimensions, left ventricular mass, and relative wall thickness in patients with white coat normotension were statistically indistinguishable from those in patients with sustained hypertension. Intergroup differences in left ventricular wall thickness and left ventricular mass remained highly significant ($P < 0.02$ to $P < 0.001$) after adjustment for covariates, whereas those for left ventricular chamber size became statistically undetectable. In parallel with these findings, left ventricular hypertrophy was present in 16% (10 of 64) of patients with sustained hypertension, 7% (4 of 61) of patients with white coat normotension, and 0.4% (1 of 234) of patients with sustained normotension ($P = 0.001$). Fractional shortening was higher in patients with sustained hypertension than in those with sustained or white coat normotension. Stroke volume was higher in patients with white coat normotension than in those with sustained normotension, but this difference was eliminated by indexation for body size.

Table 4—*Continued*

Patients with Sustained Hypertension ($n = 64$)	Difference in Mean Values between Sustained Normotension Group and Sustained Hypertension Group (95% CI)	*P* Value
0.85 ± 0.19	0.16 (0.11 to 0.22)	<0.001
5.76 ± 0.63	0.46 (0.24 to 0.69)	<0.001
17.8 ± 5.0	4.7 (3.1 to 6.3)	<0.001
0.29 ± 0.06	0.03 (0.01 to 0.05)	<0.001
17 (27)	13†	<0.05

Carotid Artery Structure and Function

The intimal–medial thickness of the common carotid artery was greater in patients with white coat normotension than in those with sustained normotension (difference of mean values, 0.10 [CI, 0.05 to 0.16]) but did not differ significantly from that in patients with sustained hypertension (difference of mean values, 0.06 [CI, −0.01 to 0.13]). Carotid lumen diameter and arterial relative wall thickness were also greater in patients with white coat normotension than in those with sustained normotension; as a result, the cross-sectional area of the carotid wall was greater in the former group. In multivariate analysis, the adjusted mean carotid wall thickness in patients with white coat normotension (0.73 ± 0.01) did not differ significantly from that in patients with sustained normotension (0.73 ± 0.02) (difference of mean values, 0.02 [CI, −0.04 to 0.07]). The adjusted mean carotid wall thickness was 0.80 ± 0.02 in patients with sustained hypertension. The mean carotid lumen diameter in patients with sustained normotension and those with white coat normotension (5.43 ± 0.57) did not differ significantly after adjustment for covariates. Discrete atherosclerotic plaques were detected in approximately twice as many patients with white coat hypertension and patients with sustained hypertension than patients with sustained normotension (**Table 4**); this finding was not statistically significant in multivariate analysis ($P > 0.2$).

Discussion

Our study provides new data on cardiac and vascular target organ damage in adults with normal clinic blood pressure and various categories of ambulatory pressure. In our population, nearly 20% of patients with clinic normotension had awake ambulatory systolic or diastolic blood pressure that exceeded previously published partition values (10). The prevalence of white coat normotension in our study was similar to that in a recent smaller study (13).

Our results extend and refine previous evidence suggesting that average ambulatory measurement of awake or 24-hour blood pressure has an important

role in predicting target organ damage (26–29) or clinical outcome (4, 6). Compared with patients with sustained normotension, patients with white coat normotension had significantly higher left ventricular wall thickness and mass. Left ventricular mass index was similar, on average, in patients with white coat normotension (86 g/m^2) and those with sustained hypertension (90 g/m^2), despite an average difference in clinic blood pressure of 35/16 mm Hg between these groups. In part, the similarity of left ventricular mass in these two groups is probably due to the smaller average difference of 14/6 mm Hg in awake ambulatory blood pressure and the known closer correlation of left ventricular mass with ambulatory blood pressure than with casual blood pressure (5, 10, 11, 26, 27). An additional factor that may contribute to the similarity of left ventricular mass in patients with white coat normotension and those with sustained hypertension is the greater stroke volume in the former group; this finding is consistent with previous documentation of stroke volume as an important stimulus that contributes to left ventricular hypertrophy (30–32).

Compared with patients with sustained normotension, patients with white coat normotension had greater carotid artery wall thickness and cross-sectional area, as well as a higher prevalence of discrete atherosclerotic plaque, although the arterial differences became insignificant in multivariate analysis. Unlike the situation with left ventricular mass, few studies have compared the impact of clinic and ambulatory pressures on arterial structure. One study (11) showed that carotid wall thickness in patients with white coat hypertension was normal, reflecting the normal ambulatory blood pressure rather than the elevated clinic pressure in these patients.

Greater obesity, higher cholesterol levels, and a trend toward more use of nicotine was seen among patients with white coat normotension compared with those with sustained normotension. The suggestive evidence of a relation between nicotine use and white coat normotension is consistent with previous data showing that smokers have a higher ambulatory blood pressure than nonsmokers (33, 34). The former associations are consistent with the known relation between overweight and arterial blood pressure and cholesterol levels. Although inverse cross-sectional relations between smoking and blood pressure, attributed to a rebound reduction in blood pressure caused by abrupt cessation of smoking during office visits, have been reported, exclusion of current smokers did not affect the statistical significance of our results.

Our findings may help to explain previous observations of clinical benefit of reducing arterial blood pressure to below the conventional partition values of 140/90 mm Hg. In the Treatment of Mild Hypertension Study (35), the event rate was lower in patients with mild hypertension and a high prevalence of overweight and dyslipidemia in whom arterial pressure was decreased to a mean of 126.7/79.4 mm Hg by medication plus lifestyle intervention than in patients whose blood pressure was decreased to 132.6/81.9 mm Hg with nutritional and hygienic intervention alone. The Hypertension Optimal Treatment trial (36) showed that diastolic blood pressure could be safely reduced to target levels less than 90 mm Hg; evidence suggested that the optimal diastolic pressure level was about 82 mm Hg. Finally, the United Kingdom Prospective Diabetes Study (37) showed that cardiovascular event rates in diabetic patients were lowest if diastolic blood pressure was reduced below 80 mm Hg. Although ambulatory blood pressure data are not available in the large randomized clinical trials, it is possible that participants in these trials who had high normal clinic blood pressure while receiving treatment had a high prevalence of ambulatory hypertension and associated target organ damage (as was seen in our unmedicated patients) that could have been reversed by further reduction of arterial pressure.

One limitation of our study is its cross-sectional, nonrandomized design. The prospective sampling of patients with normotension from specified employee groups eliminates clinical referral bias but leaves open the possibility that some patients may have chosen to participate because they knew that they had previous borderline or elevated blood pressure. Additional epidemiologic studies will be needed to define the population prevalence of white coat normotension. The use of a single measurement of ambulatory blood pressure to distinguish white coat normotension from sustained normotension may have resulted in some misclassification, although use of partition values of 134/90 mm Hg from a single set of awake blood pressure measurements has been shown to be useful in identifying patients with white coat hypertension who are at low risk for target organ damage (10, 11) and subsequent clinical events (4). Although the ability of echocardiography to measure left ventricular mass is not perfect, use of this test is supported by studies showing high correlation ($r = 0.90$) between left ventricular weight assessed by echocardiography or by necropsy (20) and high reproducibility of left ventricular mass on serial measurements (rho = 0.93) (38). Echocardiographic left ventricular hypertrophy has been consistently shown to predict high cardiovascular event rates (39, 40). This supports its use in our study as a provisional surrogate outcome. Recent data suggest that ultrasonographic detection of increased carotid wall thickness and plaque also predicts adverse outcomes (41). However, the true prognostic significance of white coat normotension must be

defined in prospective observational studies and randomized clinical trials that use actual morbid event rates. Additional research in populations large enough to stratify patients by body mass index and serum cholesterol level is needed to confirm the statistical independence from these confounders of the relation between white coat normotension and left ventricular hypertrophy. Future studies may also determine whether the subtle difference in serum creatinine level that we observed between patients with white coat normotension and those with sustained normotension reflects an underlying abnormality that could have both pressor and proatherogenic effects.

Our finding of a stepwise increase in the prevalence of white coat normotension from 11% in patients classified by JNC-V criteria as having optimal pressure to 37% in those having high-normal pressure parallels the gradient in cardiovascular risk among patients with normotension on which the JNC-V subclassification was based (17, 42). Thus, our observations may provide mechanistic insight into the occurrence of cardiovascular morbid events in patients with normotension revealed by epidemiologic research. Although our cross-sectional study supports the hypothesis that patients with white coat normotension, who have mildly elevated ambulatory pressures, represent a high-risk group, this conclusion must be regarded as tentative until long-term prospective studies determine whether white coat normotension is associated with an elevated rate of cardiovascular events. Further research is also needed to determine whether it is cost-effective to use ambulatory blood pressure recording to detect this subgroup of persons with normotension.

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